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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,451	10/24/2000	Brenda F. Baker	ISPH-0518	2604

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/695,451	Applicant(s) BAKER ET AL.	
	Examiner J. Douglas Schultz	Art Unit 1635	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-15 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed May 5, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed January 3, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

3. Applicant's arguments have been considered. Those that are rendered moot in view of the new ground(s) of rejection are not responded to. Those that are considered relevant to the new rejection are responded at the conclusion of the rejection.

Claim Rejections - 35 USC § 112

4. Claims 15 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for antisense oligos of Isis 108426 (SEQ ID NO: 189) targeted to the TNF receptor 1 (TNFR1) transcript in the treatment of hepatitis. The specification as filed does not provide guidance on the *in vivo* inhibition using any antisense molecule targeted to TNFR1 in methods of inhibiting or in treating any and all forms liver disease or injury. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of TNFR1 in human cells or tissues comprising contacting said cells or tissues with antisense compositions that inhibit the expression of TNFR1. The claims of the above invention are also drawn to methods of treating an animal having a condition associated with TNFR1, wherein said compositions are administered to animals such that expression of TNFR1 is inhibited, wherein said condition may be liver disease or injury. The language of said claims encompasses *in vivo* treatment. The specification teaches a method of using the claimed compositions to inhibit the expression of TNFR1 *in vitro* and in mice in the treatment of hepatitis using Isis 108426 .

The specification as filed does not provide any guidance or examples beyond those sequences with exemplified *in vivo* activity that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of any antisense compound *in vivo* is problematic. Thus, even though Isis 108426 has been exemplified by applicants in the treatment of a specific liver disease, the specification only provides prophetic guidance in regards to the use of any antisense compound in the treatment of any liver disease. Although applicants' specification discloses general methodologies of using the broad class of claimed constructs *in vivo* in methods of treatment, such a disclosure would not be considered enabling for such a broad genus, since the state of antisense-mediated gene inhibition is unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;

(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate that predicting the success of antisense-mediated treatments *in vivo* from tests that do not mimic or re-create *in vivo* conditions is problematic.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third

column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized

as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application does not provide adequate guidance for one of skill in the art to overcome the obstacles of predicting the success of specific sequences *in vivo* without ever having tested them in an *in vivo* analogous model system, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of TNFR1 expression *in vitro* as being correlative or representative of the successful *in vivo* use of any antisense compound in the broad treatment methods directed to any and/or all liver conditions or diseases suspected of being associated with TNFR1 expression. The specification as filed fails to provide a nexus between the problems cited and treatment achieved, beyond the sequence of Isis 108426 in the treatment of certain liver disorders.

Said claims are drawn very broadly to methods of treating cells *in vivo* or to treating or preventing any liver condition or disease suspected of being associated with TNFR1 expression

using any oligo directed to applicants instant regions of target SEQ ID NO: 1. Since the specification fails to provide any guidance for the successful treatment or prevention of such a broad range of liver diseases beyond the disclosed successful use of Isis 108426, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation in order to find any other sequences with the claimed treatment efficacy. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and /or tissues. Beyond that guidance from the specification that describes the use of Isis 108426 in the treatment of the specific liver disorder disclosed, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

5. Claims 1, 2, 5-15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**. The region recited in claim 1, nucleobases 727-1310 of SEQ ID NO: 1, does not appear to have literal support in the specification. Should

applicants disagree, applicants are invited to point out with particularity by page and line number where such support exists for antisense molecules targeting nucleobases 727-1310 of SEQ ID NO: 1 as recited in claim 1.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 and 103 that form the basis for the rejections under these sections made in this Office action:

> A person shall be entitled to a patent unless –
>
> 102(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by Brockhaus et al. (EP 0 417 563 A2).

The claims of the above invention are drawn to antisense compounds 8 to 30 nucleotides in length that specifically hybridizes with and inhibits the expression of nucleobases 727-1310 of SEQ ID NO: 1.

The nucleotide on page 31, example 1 possesses significant identity with the claimed region of SEQ ID NO:1 of the instant application, and would thus specifically hybridize with said region. Although this reference does not specifically teach the function of inhibiting applicants' instant SEQ ID NO: 1 as claimed in the present application, the above-listed

compound meets all the structural limitations as set forth in the instant claims. Because the sequence is substantially identical to applicant's claimed compounds, in the absence of evidence to the contrary said compound is thus considered to possess the functional limitations of specifically hybridizing with and inhibiting the expression of applicants' instant SEQ ID NO: 1. Support for this conclusion is drawn from MPEP 2112:

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim **but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection**. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. *Emphasis supplied.*

In rejecting the claims of the above under 35 U.S.C. 102 and 103, a prima facie case has been established by the examiner whereby the burden of proof in showing that the claimed compounds are not anticipated by the compound(s) of the prior art as stated lies with the applicant, as per MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Thus, in the absence of evidence to the contrary, the antisense compounds of claims 1 and 2 of the instant application are considered anticipated and/or obvious as outlined above.

Claim Rejections - 35 USC § 103

7. Claims 1, 2, and 5-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ojwang et al. (Biochemistry 1997, 36:6033-6045), in view of Taylor et al. (Drug Disc. Today, 1999. 4(12)562-567) and Baracchini et al. (U.S. Patent Number 5,801,154).

The invention of the above listed claims is drawn to antisense compounds that target nucleobases 727-1310 of TNFR1 and inhibit its expression, wherein said compounds may comprise internucleoside, sugar or nucleobase modifications, or wherein said compounds may be chimeric or comprise pharmaceutical compositions.

Ojwang et al. teach antisense compounds that are targeted to and inhibit the expression of TNFR1, wherein said compounds comprise phosphorothioate (internucleoside), 2'-O methyl (sugar), or C-5 propynyl (nucleobase) modifications, chimeras, and pharmaceutical (liposome) preparations. Ojwang et al. does not teach TNFR1 antisense oligos wherein the sugar and nucleobase moieties comprise 2'-methoxyethyl and 5-methylcytosine modifications respectively.

Taylor et al. teach the inhibition of expression of any protein using a known cDNA sequence to generate antisense oligos that target that and inhibit the expression of that protein, and also teach that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Baracchini et al. teaches modifications of antisense compounds comprising sugar, nucleobase, 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Baracchini et al. also teach targeting specific

regions of a gene including the coding region, and demonstrate the methods necessary to achieve gene inhibition.

It would have been obvious for one of ordinary skill in the art to target the above listed region of TNFR1, and to incorporate modifications as taught by Baracchini et al. into the antisense compounds of Ojwang et al. One would have been motivated to target said region with antisense compounds as taught by Baracchini et al., because Baracchini et al. teach that the coding region of a mRNA transcript, of which the instantly claimed region is a part of, is a desirable region to target for gene inhibition. Furthermore, one would have been motivated to target said region with antisense compounds because Ojwang indicate on page 6034, left col. Para. 3 that regions other than the start codon region may be desireable targets. Further motivation to modify the antisense oligos as instantly claimed is provided by Ojwang et al., who expressly teach modifying antisense oligos to increase resistance to degradation by incorporating several modifications that increased the bioactivity of their antisense oligo sequences, and by Baracchini et al., who further teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation. One of ordinary skill in the art would have been motivated to create such compounds to increase bioactivity because Ojwang et al. expressly teach such antisense molecules, and also teach that TNFR1 is a mediator of inflammation, and that it is an attractive target for intervention in both acute and chronic inflammatory diseases. Finally, one would have a reasonable expectation of success given that Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini et al. teach making

modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Regarding Applicants arguments that Ojwang et al. target regions other than applicants' instantly defined region, it is pointed out that applicants region is large enough to encompass the majority of the entire coding region of the molecule. Since Ojwang indicate that regions other than the coding region have been shown to have inhibitory efficacy, and because Baracchini specifically state that the coding region is a preferred targeting region, and finally because applicants claimed region of SEQ ID NO: 1 covers much if not most of the coding region, antisense molecules targeted to the region of SEQ ID NO: 1 defined by applicants are considered obvious in view of the cited art.

Applicants' state that, when viewed alone, neither of Ojwang et al. or Baracchini et al. teach or suggest antisense compounds targeted to the specific regions of the TNFR1 transcript of SEQ ID NO: 1 as presently claimed. This argument is not adopted. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is acknowledged that the references when viewed individually do not teach the presently claimed invention; however, the test for obviousness is what the *combined* teaching of the prior art would have suggested to those of ordinary skill in the art. As indicated above, one of ordinary skill in the art would have been motivated to make antisense

oligonucleotides, because the prior art teaches antisense inhibitors of TNFR1, and further teaches targeting within the same region targeted by applicants. Moreover, because Baracchini et al. teach that synthesizing and using antisense oligos to inhibit transcripts of known sequence is routine to one of ordinary skill in the art, this combination also provides a reasonable expectation of success which render the invention of the claims above obvious under 35 U.S.C. § 103(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
July 11, 2003

KAREN LACOURCIERE
PATENT EXAMINER